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EXAMINER	
GAKH, YELENA G	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/765,264	PAPPIN ET AL.	
	Examiner	Art Unit	
	Yelena G. Gakh, Ph.D.	1797	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 March 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-114* is/are pending in the application.

4a) Of the above claim(s) *9-13, 16, 18-19, 26, 30-33, 35, 38-41, 44-46, 93-94, 96-97, 99, 101, 105-106, 110-111 and 113* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *See Continuation Sheet* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *08/09/04, 12/30/04, 05/15/06, 07/03/06, 09/22/06, 01/16/07, 05/04/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims rejected are 1-8,14,15,17,20-25,27-29,34,36,37,42,43,47-92,95,98,100,102-104,107-109,112 and 114.

DETAILED ACTION

1. Election of species recited in claims 1-8, 14-15, 17, 20-25, 27-29, 34, 36-37, 42-43, 47-92, 95, 98, 100, 102-104, 107-109, 112, and 114, N-hydroxysuccinimide ester in claim 21 and piperazine or piperadine in claims 25 and 98 with traverse, filed on 03/31/08, is acknowledged. Claims 1-114 are pending in the application. Claims 9-13, 16, 18-19, 26, 30-33, 35, 38-41, 44-46, 93-94, 96-97, 99, 101, 105-106, 110-111 and 113 are withdrawn from consideration. Since no arguments regarding restriction requirements were provided, the examiner considers this election to be made without traverse and thus FINAL.

Specification

2. The following guidelines illustrate the preferred layout for the specification of a utility application. These guidelines are suggested for the applicant's use.

Arrangement of the Specification

As provided in 37 CFR 1.77(b), the specification of a utility application should include the following sections in order. Each of the lettered items should appear in upper case, without underlining or bold type, as a section heading. If no text follows the section heading, the phrase "Not Applicable" should follow the section heading:

(a) TITLE OF THE INVENTION.
(b) CROSS-REFERENCE TO RELATED APPLICATIONS.
(c) STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT.
(d) THE NAMES OF THE PARTIES TO A JOINT RESEARCH AGREEMENT.
(e) INCORPORATION-BY-REFERENCE OF MATERIAL SUBMITTED ON A COMPACT DISC.
(f) BACKGROUND OF THE INVENTION.
    (1) Field of the Invention.
    (2) Description of Related Art including information disclosed under 37 CFR 1.97 and 1.98.
(g) BRIEF SUMMARY OF THE INVENTION.
(h) BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWING(S).
(i) DETAILED DESCRIPTION OF THE INVENTION.
(j) CLAIM OR CLAIMS (commencing on a separate sheet).
(k) ABSTRACT OF THE DISCLOSURE (commencing on a separate sheet).
(l) SEQUENCE LISTING (See MPEP § 2424 and 37 CFR 1.821-1.825. A "Sequence Listing" is required on paper if the application discloses a nucleotide or amino

acid sequence as defined in 37 CFR 1.821(a) and if the required "Sequence Listing" is not submitted as an electronic document on compact disc).

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to as not containing a written description of the invention "in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same".

The specification is not arranged in the manner provided by the guidance, which ensures a clear and concise description of the invention, and in general is written in unclear and vague language in regards to the subject matter considered by the Applicants as inventive and non-obvious over the prior art. The specification does not contain a Summary of the Invention which allows understanding, as to what specifically the Applicants consider the essence of their invention. In combination with the vague and indefinite language of the claims, which recite "a method, comprising" reacting two or more samples with reactive analytes and mixing the products of the reaction (e.g. Claim 1), the specification does not meet the requirements of the first paragraph of 35 U.S.C. 112. The description of the "Field of the Invention" as "analyte determination by mass analysis" is so general and broad, that it does not reflect to any extent the inventive subject matter. The only specific disclosure provided in the specification in regards to the claimed subject matter is related to specific examples, which therefore will be considered as the only enabling disclosure of the instant application. In other words, the only enabling disclosure is pertained to specific examples, which disclose proteomic analysis based on mass spectrometry of specifically labeled proteins with the labels provided in the examples and the proteins being extracted, digested and separated. Moreover, not all specific labels disclosed in the specification enable performing the method, since e.g. there is no experimental evidence for thiocarbonyl linker to be capable of providing the function required by the instant method, taking into account the reactivity of thiocarbonyl compounds (see page 50, lines 12-17).

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-8, 14-15, 17, 20-25, 27-29, 34, 36-37, 42-43, 47-92, 95, 98, 100, 102-104, 107-109, 112, and 114 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The MPEP states that the purpose of the written description requirement is to ensure that the inventor had possession, as of the filing date of the application, of the specific subject matter later claimed by him. The courts have stated:

> "To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." *Lockwood v. American Airlines,Inc..*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); *In re Gosteli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (" [T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d at 1572, 41 USPQ2d at 1966." *Regents of the University of California v. Eli Lilly & Co.*, 43 USPQ2d 1398".

The MPEP lists factors that can be used to determine if sufficient evidence of possession has been furnished in the disclosure of the Application. These include "level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention. Disclosure of any combination of such identifying characteristics that distinguish the claimed invention from other materials and would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed species is sufficient." MPEP 2163.

Further, for a broad generic claim, the specification must provide adequate written description to identify the genus of the claim. *In Regents of the University of California v. Eli Lilly & Co.,* the Court stated:

> "A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials. Fiers_, 984 F.2d at 1171, 25 USPQ2d at 1606; In re Smythe, 480 F.2d 1376, 1383, 178 USPQ 279, 284-85 (CCPA 1973) ("In other cases, particularly but not necessarily, chemical cases, where there is unpredictability in performance of certain species or subcombinations other than those specifically enumerated, one skilled in the art may be found not to have been placed in possession of a genus .... "). *Regents of the University of California v. Eli Lilly & Co.*, 43 USPQ2d 1398.

The MPEP further states that if a biomolecule is described only by a functional characteristic, without any disclosed correlation between function and structure of the sequence, it is "not sufficient characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence." MPEP 2163. The MPEP does state that for generic claim the genus can be adequately described if the disclosure presents a sufficient number of representative species that encompass the genus. MPEP 2163. If the genus has a substantial variance, the disclosure must describe a sufficient variety of species to reflect the variation within that genus. See MPEP 2163. Although the MPEP does not define what constitute a sufficient number of representative, the Courts have indicated **what do not** constitute a representative number species to adequately describe a broad generic. In *Gostelli*, the Court determined that the disclosure of two chemical compounds within a subgenus did not describe that subgenus. *In re Gostelli*, 872 F.2d at 1012, 10 USPQ2d at 1618.

In the instant application e.g. claim 1 recites reacting two or more samples comprising reactive analytes with a different labeling reagent of the formula RP-X-LK-Y-RG, with the most broad definition of RG, "a reactive group that is an electrophile capable of reacting with one or more of the reactive analytes"; RP, "a reporter moiety that links the reactive group and the reporter group, and which comprises a fixed charge or that is ionizable", with the only specific recitation provided for the LK, the linker group, which has one of the specific formulas recited in the claim. The recitation for the reporter RG contradicts its definition provided by the specification which discloses: "[t]he reporter moiety of the labeling reagent or reagents used in the method, mixture, kit and/or composition embodiments is a group *that has a unique mass (or*

mass to charge ratio) that can be determined. Accordingly, each reporter of a set can have a unique gross mass. *Different reporters can comprise one or more heavy atom isotopes to achieve their unique mass*" (page 9, lines 19-22). The recitation for the reporter RG in the claims is much broader and encompasses many more embodiments then what is disclosed in the specification, and therefore is not supported by the written disclosure.

Furthermore, the claims are drawn to a method, but do not specify for what purpose; therefore they are open to any kinds of methods that may use such reagents, which is beyond the scope of proteomic analysis and quantitation as exemplified in the instant application (page 4, lines 6-7) The specification does provide examples of what qualify as method within the claimed invention (see, e.g. pages 56-58); however, these are limited to a few examples such as using the N-methyl piperazine compounds of Figure 8. As stated earlier, the MPEP states that written description for a genus can be achieved by a representative number of species within a broad generic. The possible structural variations of the method formula are limitless to any class of reactive group that is electrophilic or nucleophilic, conjugated with any reporter moiety that has a mass that can be measured.

In addition, the term analyte within the instant method is defined on page 4, lines 12-29:

> "As used herein, "analyte" refers to a molecule of interest that may be determined. Non-limiting examples of analytes include, but are not limited to, proteins, peptides, nucleic acids (both DNA or RNA), carbohydrates, lipids, steroids and other small molecules with a molecular weight of less than 1500 Daltons (Da). The source of the analyte, or the sample comprising the analyte, is not a limitation as it can come from any source. The analyte or analytes can be natural or synthetic. Non-limiting examples of sources for the analyte, or the sample comprising the analyte, include cells or tissues, or cultures (or subcultures) thereof. Non-limiting examples of analyte sources include, but are not limited to, crude or processed cell lysates, body fluids, tissue extracts, cell extracts or fractions (or portions) from a separations process such as a chromatographic separation, a 1D electrophoretic separation, a 2D electrophoretic separation or a capillary electrophoretic separation. Body fluids include, but are not limited to, blood, urine, feces, spinal fluid, cerebral fluid, amniotic fluid, lymph fluid or a fluid from a glandular secretion. By processed cell lysate we mean that the cell lysate is treated, in addition to the treatments needed to lyse the cell, to thereby perform additional processing of the collected material. For example, the sample can be a cell lysate comprising one or more analytes that are peptides formed by treatment of the cell lysate with a proteolytic enzyme to thereby digest precursor peptides and/or proteins".

However, the examples presented are drawn exclusively to analytes that are peptides/proteins extracts from cell lysates, which are digested and separated (see Examples 3-5) and no other analytes were exemplified therein. MPEP states that if a biomolecule (such as the

instantly claimed analyte) is described only by a functional characteristic (such as being capable of reacting with RG), without any disclosed correlation between function and structure of the sequence, it is "not sufficient characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence." MPEP 2163. Here, though the claims may recite some functional characteristics, the claims lack written description because there is no disclosure of a correlation between function and structure of the analytes beyond those disclosed in the examples in the specification. Moreover, the specification lacks sufficient variety of species to reflect the variance in the RP-X-LK-Y-RG /analyte genus since the specification does not provide any examples of conjugates with e.g., specific RP-X-LK-Y-RG used to analyze nucleic acids (both DNA or RNA), carbohydrates, lipids, steroids and other small molecules with a molecular weight of less than 1500 Daltons (Da) and so forth. The description requirement of the patent statute requires a description of an invention, not an indication of a result that o.ne mighi achieve if one made that invention. See *In re Wilder*, 736 F.2d 1516, 1521, 222 USPQ 369, 372-73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin[e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate.").

Accordingly, it is deemed that the specification fails to provide adequate written description for the genus of the claims and does not reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the entire scope of the claimed invention.

6. Claims 1-8, 14-15, 17, 20-25, 27-29, 34, 36-37, 42-43, 47-92, 95, 98, 100, 102-104, 107-109, 112, and 114 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the method of proteomic analysis based on mass spectrometry of isobarically tagged peptides, obtained by separate digestion of cellular proteins extracts and separately reacted with different isobaric reagents, with the isobarically labeled tags specified on Figures 1-2 and 8, does not reasonably provide enablement for any other method. It would have been an undue experimentation for a person of ordinary skill in the art to develop a method, which is not directed toward proteomic analysis based on mass spectrometry of isobarically tagged peptides obtained as disclosed in the specific examples in the instant specification, or with any other labeled tags besides those indicated in the examples. The specification does not

provide any guidance for a routineer in the art to practice the invention within the scope of the claims; neither does it disclose other examples for analytes not being proteins or peptides, or any isobarically tagged reagents.

Claims 42, 43, 49 and 112 are further rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the method, in which the sample mixture comprises at least one of the *pairs* of isobarically tagged analytes, does not reasonably provide enablement for the method, involving only one of such analytes, since one isotopically tagged analyte cannot be isobarically tagged. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims. In order for the analyte to be "isobarically" tagged, there should be another analyte tagged with an isobaric isomer, to the examiner's understanding.

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 1-8, 14-15, 17, 20-25, 27-29, 34, 36-37, 42-43, 47-92, 95, 98, 100, 102-104, 107-109, 112, and 114 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims recite "a method comprising" reacting two or more samples with reagents and mixing the samples. The second paragraph of 35 U.S.C. 112 recites "the specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention". MPEP 2171 states:

> "[t]here are two separate requirements set forth in this paragraph: (A) the claims must set forth the subject matter that applicants regard as their invention; and (B) the claims must particularly point out and distinctly define the metes and bounds of the subject matter that will be protected by the patent grant. The first requirement is a subjective one because it is dependent on what the applicants for a patent regard as their invention. The second requirement is an objective one because it is not dependent on the views of applicant or any particular individual, but is evaluated in the context of whether the claim is definite — i.e., whether the scope of the claim is clear to a hypothetical person possessing the ordinary level of skill in the pertinent art".

It appears that the instant claims do not meet either of the requirements of the second paragraph of 35 U.S.C. 112. From the claim language it is not clear neither what is the subject matter that the applicants regard as their invention, nor it is clear to a hypothetical person

possessing the ordinary skill in the pertinent art, as to what is the scope of the claims. It is not apparent from the claims, as to whether any method that incorporates reacting analytes with the labels of claim 1 and mixing the products is considered to be the Applicants invention, or whether all possible analytes can be analyzed with the recited method. The claims do not specify, as to what is the purpose of the method, and the scope of the claims is not defined by the language of the claims, since an infinite plethora of embodiments meets the limitations of the claims.

The language of claim 1 is further not clear and definite, since it is not clear, as to how it is possible to perform the step of "reacting two or more different samples with *a different labeling reagent*"? If this is just one labeling reagent, then what is it different from? It appears from the claim that all "different reactive analytes" react with the same labeling reagent, which does not make much sense. Moreover, such reaction would not produce isobarically labeled samples, since all samples will be labeled with the same label, and they will be different from each other only because of their original differences. Also, it is not apparent, as to how isobarically labeled samples can be produced, if no isobarically different reagents are used in the reaction?

Furthermore, the language of claim 1 is not clear and definite in regards to the reference to the compensation of the gross mass between reporters for different labeling reagents with the linker that has a very specific structural formula. The language of the claim does not define anyhow a relation between different labeling reagents, and therefore it is not apparent, as to how the linker of a certain structural formula can compensate for the gross mass between reporters, which may have e.g. different structures. If such compensation occurs because of proper isotopic labeling of the linker corresponding to the isotopic labeling of the reporter, this needs to be clearly recited in the claim. No isotopic labeling of the reporters is recited in the claims.

Also, the word "labeling" appears to be misleading in the context of the claims, since the expression "isobarically labeled samples" could mean that the samples themselves are isotopically labeled, rather than tagged with isotopically labeled reagents. Especially confusing this terminology is in the claims reciting specifically tagged analytes. It appears that in the instant application the words "tag" and "label" should not be synonyms, contrary to the definition given in the specification, since e.g. reporter moieties and linkers are isotopically labeled, while

the analytes are tagged with isotopically labeled reagents. The examiner respectfully requests the Applicants to amend the claims to make it clearer, as to what is isotopically labeled, and what is tagged with isotopically labeled reagents. The most confusing term is "isobarically labeled analytes", which conventionally would mean that the analytes themselves are isotopically labeled so that they would have the same gross mass, which is not the case in the instant application.

Claims 42, 43, 49 and 112 recite "one or more isobarically labeled analytes". To the examiner's understanding, isobaric labeling assumes labeling of the analytes with at least two isobaric isomers, since "isobaric" is a relative term, which has meaning only when two compounds compare to each other (two compounds have the same structure and the gross mass, but different isotope distribution). It does not seem that the expression "isobaric labeling" has a sensible meaning when refers to just one compound. In this case it will be just a conventional isotopic enrichment (labeling).

Claim 48 recites contradictory subject matter. First, it is not apparent, as to how the solid support can have the formula E-F-RP-X-LK-Y-RG, and at the same time be a part of the same formula (E). The examiner believes, that the proper preamble should recite something like "the method of claim 47, wherein each different labeling reagent of the set is attached to the solid support E according to the formula: E-F-RP-X-LK-Y-RG". Second, the structural formula RP-X-LK-Y-RG is predetermined by the recitation of claim 1, and therefore should correspond to this recitation. Claim 1 recites RG as an electrophile, and not nucleophile, and therefore RG of claim 47 does not have an antecedent basis. Furthermore, since all fragments of the formula are already recited in claim 1, it appears that there is no necessity to repeat the same recitation in claim 48. Claim 48 has the same problems as claim 1, which were described above.

Claim 48 can be re-written in a much simpler form, if the recitation of the parent claim will not be repeated. The same is true for claim 49, which can be made dependent on claim 43 the same way as claim 48 depends on claim 1.

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

11. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

12. **Claims 1-8, 14-15, 17, 20-24, 27-29, 34, 36, 47, 50-92, 95, 100 and 114** are rejected under 35 U.S.C. 103(a) as being unpatentable over Schmidt et al. (US 2003/0194717A1).

Schmidt discloses a method of tandem mass spectrometry for isotopically and isobarically labeled analytes, including proteins, peptides, nucleotides, which inherently comprises the steps of reacting two or more samples comprising reactive analytes with mass labels. Schmidt discloses the following:

> "Provided is a set of two or more mass labels, each label in the set comprising a mass marker moiety attached via a cleavable linker to a mass normalisation moiety, the mass marker moiety being fragmentation resistant, wherein the aggregate mass of each label in the set may be the same or different and the mass of the mass marker moiety of each label in the set may be the same or different, and wherein in any group of labels within the set having a mass marker moiety of a common mass each label has an aggregate mass different from all other labels in that group, and wherein in any group of labels within the set having a common aggregate mass each label has a mass marker moiety having a mass different from that of all other mass marker moieties in that group, such that all of the mass labels in the set are distinguishable from each other by mass spectrometry" (Abstract).
> The general structural formula for the label is: $\mathbf{M(A)_y\text{-}L\text{-}X(A)_z}$

> "wherein M is the mass normalisation moiety, X is the mass marker moiety, A is a mass adjuster moiety, L is a cleavable linker, y and z are integers of 0 or greater, and y+z is an integer of 1 or greater. Preferably M is a fragmentation resistant group, L is a linker that is susceptible to fragmentation on collision with another molecule or atom and X is preferably a pre-ionised, fragmentation resistant group. The sum of the masses of M and X is the same for all members of the set. Preferably M and X have the same basic structure or core structure, this structure being modified by the mass adjuster moieties" [0048].
> "[0049] The mass adjuster moiety ensures that the sum of the masses of M and X in is the same for all mass labels in a set, but ensures that each X has a distinct (unique) mass".

Preferably, cleavable linker comprises amide bond ([0070]), i.e. it comprises the fragment C=O (Claim 28).

One of the examples of labeling oligonucleotides including isobaric tagging: "[w]hen these molecules are analysed by mass spectrometry, they can be combined with a complementary component to give 9 [nine] isobaric tags which can be analysed in a tandem instrument" ([0204].

Performing tandem mass spectrometric analysis disclosed by Schmid corresponds to the recitation of claims 2-5.Schmidt further discloses:

> "[0112] The property of the analytes is not particularly limited. However, in this embodiment in step (a) and/or step (b) the analytes are preferably separated according to their length or mass. It is further preferred that in step (a) and/or step (b) the analytes are separated according to their iso-electric point. Typically, the analytes comprise one or more proteins, polypeptides, peptides, amino acids or nucleic acids, or fragments thereof. It is particularly preferred that gel electrophoresis is employed in each of the separation steps. In this embodiment, the method is a method of 2-dimensional gel electrophoresis."

Conventionally peptides are the products of enzymatic, specifically proteolytic trypsin, digestion reaction (Claims 6-9, 14, 15). Specific steps of purification, digestion proteins to peptides, separating, reacting peptides with labels including reaction of "an amine-reactive N-hydroxysuccinimide ester linked to a thiol-reactive vinyl sulphone moiety" are disclosed in paragraphs [0305]-[0309]. "The compound reacts very easily with amines via the ester functionality without reaction of the vinyl sulphone and can be separately reacted with thiols at a later stage"([0309]) (claims 20-21). The reporters can be benzyl groups (see [0177]-[0179]) (Claims 22-24). Paragraph [0218] discloses immobilizing the tagged analytes on the solid support.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Yelena G. Gakh, Ph.D. whose telephone number is (571) 272-1257. The examiner can normally be reached on 9:30 am - 6:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jill A. Warden can be reached on (571) 272-1267. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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